INTERVIEW

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Tracks 1-11

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Track 2	**Case discussion:** A 45-year-old woman with TNBC and blastic bone metastases whose disease progresses after first-line chemotherapy experiences disease stabilization after receiving enzalutamide on a clinical trial
Track 3	Potential role of radium-223 dichloride in treating bone metastases in BC
Track 4	Immune checkpoint blockade for patients with TNBC
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Track 10	Activity of eribulin as first-line therapy for patients with mBC
Track 11	**Case discussion:** A 50-year-old woman with heavily pretreated ER-positive/HER2-positive PIK3CA-mutant mBC achieves an excellent response to eribulin and trastuzumab

Select Excerpts from the Interview

Track 1

DR LOVE: What is the role of androgen receptor (AR) antagonists in the management of mTNBC?

DR O'SHAUGHNESSY: Targeting AR in mTNBC is an important strategy. Recently, we saw the effects of a powerful pure AR antagonist, enzalutamide, in mTNBC. As a single agent, enzalutamide elicited an impressive clinical benefit rate of 39% at 16 weeks in patients with advanced AR-positive TNBC (Traina 2015; [3.1]).

I was interested in the results of the enzalutamide study because the investigators had access to the "PREDICT AR" gene expression assay. The PREDICT AR assay enables us to take patients with AR-positive TNBC and ask, "Which individuals have AR as a driving transcription factor in their disease?" The assay seems to be better than measuring AR by IHC testing for staining greater than 10%. Most patients with PREDICT AR-positive disease tend to have higher expression of AR. However, some

3.1

MDV3100-11: Efficacy and Safety Results of a Phase II Trial of Enzalutamide for Patients with Advanced Androgen Receptor (AR)-Positive, Triple-Negative Breast Cancer

		Intention-to-treat (ITT) population according to PREDICT AR status*	
Efficacy	**Evaluable patients** (n = 75)	**AR-positive** (n = 56)	**AR-negative** (n = 62)
CR/PR	8%	9%	3%
CBR at 16 weeks	35%	39%	11%
CBR at 24 weeks	29%	36%	6%
Median PFS	14.7 weeks	16.1 weeks	8.1 weeks
Median OS	NR	NYR	32.1 weeks
TRAEs in ITT (n = 118)	**All grades**	**Grade ≥3**	
Fatigue	34%	5%	
Nausea	25%	0%	
Constipation	8%	1%	
Back pain	2%	1%	
Dyspnea	4%	1%	

CR = complete response; PR = partial response; CBR = clinical benefit rate; PFS = progression-free survival; OS = overall survival; NR = not reported; NYR = not yet reached; TRAEs = treatment-related adverse events

* PREDICT AR is a genomic signature associated with androgen biology to predict response to enzalutamide in triple-negative breast cancer.

Safety data were consistent with the known profile of enzalutamide.

Traina TA et al. *Proc ASCO* 2015;**Abstract 1003**.

patients with disease categorized as PREDICT AR-positive express lower levels of AR by immunohistochemistry.

Once we have more data about patients who would benefit most from enzalutamide, we must conduct clinical trials in early metastatic disease and for patients at high risk in the adjuvant setting. This will include patients with TNBC and the 50% of patients with ER-negative, HER2-positive, AR-positive breast cancer.

Track 4

DR LOVE: Would you discuss your perspective on the results of the trials evaluating the safety and efficacy of immune checkpoint inhibitors in TNBC?

DR O'SHAUGHNESSY: In the Phase Ib KEYNOTE-012 trial of pembrolizumab, an anti-PD-1 antibody, in patients with advanced TNBC, an overall response rate of approximately 19% was reported (Nanda 2014). Some of the responses were unquestionably more durable than we would ever see with chemotherapy in heavily pretreated disease. Pembrolizumab has excellent tolerability. The safety issues in terms of serious pneumonitis and colitis are not as apparent as they are with ipilimumab. Both pembrolizumab and the anti-PD-L1 antibody atezolizumab (MPDL3280A) (Emens 2014) appear active in trials focusing on patients with PD-L1-positive mTNBC.

I believe we need a better handle on the subset of patients who will benefit most from these agents. The Phase II KEYNOTE-086 trial of pembrolizumab monotherapy for patients with mTNBC is currently ongoing (NCT02447003). I am excited about this trial because all patients with mTNBC will be able to receive this agent. It includes a cohort of patients with PD-L1-negative disease and another with PD-L1-positive TNBC. It will be a large trial, and lots of data will be collected in terms of which patients have the potential for substantial benefit from treatment.

Tracks 8-10

DR LOVE: The recently published results of the Phase III CALGB-40502 trial for patients with chemotherapy-naïve advanced breast cancer demonstrated that weekly nanoparticle albumin-bound (*nab*) paclitaxel was not superior to weekly solvent-based paclitaxel (Rugo 2015). What are your thoughts on administering *nab* paclitaxel in this population of patients in your practice?

DR O'SHAUGHNESSY: I predominantly administer weekly *nab* paclitaxel as a toxicity reduction strategy to avoid chronic steroid use with regular paclitaxel, which causes extreme fatigue for patients over time. We have preclinical data and ongoing clinical trials that are evaluating glucocorticoid receptor (GR) blockade. Also, it has been shown that steroids signal through GR in TNBC and that this leads to drug resistance. An ongoing Phase I trial is evaluating mifepristone, a GR antagonist, and eribulin in mTNBC (NCT02014337).

We conducted a large Phase II trial in later-line mBC in which we evaluated weekly *nab* paclitaxel at 100 or 125 mg/m^2 on a 3-week-on, 1-week-off schedule. In our experience, only 8% of patients experienced Grade 3 peripheral neuropathy at 100 mg/m^2 (Blum 2007) compared to 24% Grade 3 peripheral neuropathy with weekly paclitaxel at 80 mg/m^2 observed in the earlier-line setting. On this basis, I believe I get more mileage using weekly *nab* paclitaxel with less peripheral neuropathy.

DR LOVE: What is your perspective on the results of the Phase III GeparSepto trial comparing *nab* paclitaxel to solvent-based paclitaxel as part of neoadjuvant chemotherapy for patients with early breast cancer (Untch 2014)?

DR O'SHAUGHNESSY: The results are interesting and encouraging, indicating that the pCR rate is significantly higher with *nab* paclitaxel (38%) versus solvent-based paclitaxel (29%) when administered on a weekly basis before anthracycline-based chemotherapy. I would like to see an accelerated approval of *nab* paclitaxel in this setting based on the pCR rates.

DR LOVE: Can you comment on the role of eribulin for patients with HER2-positive advanced breast cancer?

DR O'SHAUGHNESSY: As first-line therapy in HER2-positive advanced breast cancer, eribulin in combination with trastuzumab produced a respectable objective response rate of 71.2% in a Phase II trial. The median PFS overall was 11.6 months. These patients experienced more Grade 3 or higher neuropathy than is normally observed in later-line therapy because they received eribulin for a long time (Wilks 2014; [3.2]). Eribulin is a highly active agent. It rivals any of the other strategies for first-line metastatic disease. It is another agent that can be safely and effectively combined with trastuzumab. The results of this study have given me the license to use it in later-line HER2-positive metastatic disease.

3.2

Efficacy and Safety of Eribulin in Combination with Trastuzumab as First-Line Therapy for HER2-Positive Locally Recurrent or Metastatic Breast Cancer

Response	Eribulin/trastuzumab (n = 52)	
Objective response rate	37 (71.2%)	
Complete response	3 (5.8%)	
Partial response	34 (65.4%)	
Median DoR	11.1 months	
Median PFS		
All patients (n = 52)	11.6 months	
ER-positive (n = 35)	13.1 months	
ER/PR-negative (n = 15)	9.5 months	
Adverse events (n = 52)	**All grades**	**Grade ≥3**
Fatigue	36 (69.2%)	4 (7.7%)
Peripheral neuropathy	36 (69.2%)	14 (26.9%)
Neutropenia	31 (59.6%)	20 (38.5%)
Febrile neutropenia	4 (7.7%)	4 (7.7%)

DoR = duration of response; PFS = progression-free survival

Wilks S et al. *Clin Breast Cancer* 2014;14(6):405-12.

A Phase II study of eribulin for patients with advanced HER2-negative breast cancer demonstrated a response rate of approximately 30% and a median PFS of approximately 7 months (McIntyre 2014). An ongoing Phase III trial is comparing eribulin to standard weekly paclitaxel as first- or second-line therapy for HER2-negative locally recurrent or metastatic breast cancer (NCT02037529). This will provide data on whether eribulin is an agent that will have benefit compared to weekly standard-formulation paclitaxel in HER2-negative advanced disease. ■

SELECT PUBLICATIONS

Blum J et al. **Phase II study of weekly albumin-bound paclitaxel for patients with metastatic breast cancer heavily pretreated with taxanes.** *Clin Breast Cancer* 2007;7(11):850-6.

Emens LA et al. **Inhibition of PD-L1 by MPDL3280A leads to clinical activity in patients with metastatic triple-negative breast cancer.** San Antonio Breast Cancer Symposium 2014;**Abstract PD1-6**.

McIntyre K et al. **Phase 2 study of eribulin mesylate as first-line therapy for locally recurrent or metastatic human epidermal growth factor receptor 2-negative breast cancer.** *Breast Cancer Res Treat* 2014;146(2):321-8.

Nanda R et al. **A phase Ib study of pembrolizumab (MK-3475) in patients with advanced triple-negative breast cancer.** San Antonio Breast Cancer Symposium 2014;**Abstract S1-09**.

Rugo HS et al. **Randomized phase III trial of paclitaxel once per week compared with nanoparticle albumin-bound *nab*-paclitaxel once per week or ixabepilone with bevacizumab as first-line chemotherapy for locally recurrent or metastatic breast cancer: CALGB 40502/NCCTG N063H (Alliance).** *J Clin Oncol* 2015;33(21):2361-9.

Untch M et al. **A randomized phase III trial comparing neoadjuvant chemotherapy with weekly nanoparticle-based paclitaxel with solvent-based paclitaxel followed by anthracyline/cyclophosphamide for patients with early breast cancer (GeparSepto); GBG 69.** San Antonio Breast Cancer Symposium 2014;**Abstract PD2-6**.